INTERNATIONAL CORNER

STATE OF ART ON POSTMENOPAUSAL OSTEOPOROSIS

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INTRODUCTION

Osteoporosis is frequently under-recognized by physicians despite its relevance for public health and health costs. It is essentially a "female disease" (with lower fracture risk for men) and it is part of the "menopausal syndrome". The sexual dimorphism of osteoporosis is due to the role of estrogen postmenopausal deprivation. A similar "hormonal risk factor" is not present in men, although both male and female sex hormones are strong osteoprotective factors. Several evidences (1-4) confirmed that (i) higher incidence of osteoporosis is presente after menopause; (ii) spontaneous menopause leads to increased osteoclastic activity and bone resorption uncompensed by osteoblastic activity , (iii) acute and complete estrogen deprivation, as in bilateral ovariectomy, leads to a fast bone loss, (iv) the marked bone loss particularly evident during the first 4-5 years after last menstruation, eventually results into skeletal fragility with high risk for minimal trauma fracture; (v) skeletal sites rich in cancellous bone (vertebrae, femur and radious) are particularly involved; (vi) estrogens "in vitro" inhibit osteoclastic activity; (vii) substitutive administration of estrogens limits bone resorption, restoring the physiological rate of bone loss.
The life-time risk for fracture at vertebrae, hip and distal radious is 30-50% in women (but only 15-30% in men) and much higher than risk for cardiovascular diseases and cancer (5-12% and 30-40%, respectively) explaining clearly the relevance of the disease. The annual global cost for osteoporotic fractures in USA is estimated to attain 30-40 billions of Euro in 2020, because of the increase in life span of population. One third of these expenses depends on femur fractures, including direct intervention and morbidity costs. These considerations greatly reinforced interest in osteoporosis to limit disabilities and financial impact through diagnostic and therapeutic prevention. In this review I will overview this topics in a practical perspective to help gynecologists towards a correct preventive management.

DIAGNOSTICS

Ideal preventive diagnosis of osteoporosis should be achieved before appearance of clinical fractures which mark severe and irreversible osteoporotic process. Osteoporosis is chiefly a diminution of bone mass per unit of bone volume. According to the the definition of NIH Consensus Development Conference in 1993 (5), it is "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with consequent increase in bone fragility and a susceptibility to fracture". Although the bone biopsy is the only specific method for diagnosis before fracture appears, this is not suitable in the current clinical practice. The quantification of bone mass as bone density by densitometric techniques brought about a new classification in 1994 by World Health Organization (Table 1) (6), and a new NIH statement to define osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of 2 main features: bone density and bone quality" (7).
Diagnostic management of postmenopausal osteoporosis includes: (i) evaluation of osteoporosis risk (i.e. risk to develop low bone mass in apparently healthy women); (ii) evaluation of fracture risk (i.e. risk to develop fragility fractures mainly in women with low bone mass) and (iii) diagnosis of osteoporosis.
Risk evaluation is not a clinical diagnosis of disease, but a "multifactorial clinical evaluation" of probability of a future pathology. In the case of osteoporosis it includes evaluation of risk of osteoporosis and of risk of fracture and is largely based on the use of epidemiologic and anamnestic predictors. In contrast diagnosis of osteoporosis is the detection of the disease and is based on clinical and instrumental data, and on laboratory measurements.

Evaluation of osteoporosis risk

Predicting factors for osteoporosis risk (Table I) are essentially anamnestic and include primary factors (age and menopause); lifestyle factors; secondary factors (i.e. those related to other disease conditions) and, finally, genetic and constitutional factors. In addition, bone density (which is commonly employed as categorical variable for diagnosis of osteoporosis) can be used, as continuous variable, for osteoporosis prediction (i.e. selection of "high risk" women) and criteria are available in this perspective. The high cost, the exposition to radiation and the complexity of x-rays based densitometric technologies (Double Energy X-rays Absorptiometry – DEXA), used in bone density analysis, limit the use of this predictor in the evaluation of the osteoporotic risk among general population, but anamnestic criteria are available to target women to DEXA (8). A good performing one is "OST score" when higher than 2 (9). However, only confirmation of "high risk" in osteopenic patients by DEXA authorizes starting of osteoprotective therapy (Table II). Along with clinical risk factors, attention should be paid to biochemical bone markers to identify fast bone losers at high risk for osteoporosis .

Table I. Main clinical risk factors for osteoporosis (i.e. very low bone density)

- Primary factors:
  - Aging; menopause
- Life-style related factors:
  - Low calcium intake; smoke; alcohol; low physical activity
- Secondary factors:
  - *Medications* (corticosteroids, phenytoin, gonadotropin releasing hormone agonists, loop diuretics, methotrexate, thyroid, heparin); *Hereditary skeletal diseases* (osteogenesis imperfecta, rickets, hypophosphatasia); *Endocrine and metabolic diseases* (hypogonadism, hyperparathyroidism, hyperthyroidism, Cushing syndrome, acidosis, Gaucher's disease); *Malnutrition conditions* (anorexia, intestinal malabsorption, cystic fibrosis); *Marrow diseases* (myeloma, mastocytosis, thalassemia); *Other* (renal insufficiency, hypercalciuria; hepatic disease, systemic lupus)
- Genetic risk factors:
  - Ethnicity (caucasian and asian); Body size (small frame); thinness; family history; low body weight.

Evaluation of fracture risk

Also evaluation of fracture risk is multifactorial including anamnestic and skeletal predictors (Table III). Anamnestic predictors should be investigated in all women, since over 50% of minimal trauma fractures at the specific skeletal sites of postmenopausal osteoporosis (vertebrae, hip) occurs with normal bone density. This indicates that other factors influence bone fragility and fracture risk along with bone density. According to last NIH consensus (7) bone density and bone quality are the main skeletal predictors of the fracture risk. Bone density is a strong predictor as extensively documented in prospective studies. A meta-analysis performed by Marshall et al. (10) definitively established the relationship. In addition, bone quality is classified as a major skeletal fracture risk factor in the above NHI statement (7). Best information on bone architecture is offered by ultrasound techniques with apparent relation to fracture risk (11). Literature data suggest that increased metabolic resorption also correlates significantly and directly with fracture risk. However, bone density, quality and turnover values, by themselves, are still only a piece of the clinical information about the fracture risk. Other fracture risk factors are occurence of previous fracture, age and life-expectancy. In 2004, Kanis , as spearheading for the WHO Scientific Group Meeting on Fracture Risk (12), reported the independent risk factors for fracture validated in 8 international cohorts studies with 60.000 women evaluated over 10 years (Table III). These studies included

Table II. Decisional criteria for pharmacological active prevention in "high risk" osteopenic women or for therapy of osteoporosis (adapted from suggestions of National Osteoporosis Foundation (NOF), North American Menopause Society (NAMS) and Dr. J.A.. Kanis) (20-22)

NOF, 2003	NAMS, 2002
Preventive therapy ("high risk osteopenia"): • When T-score (vertebral/femural) is between –1.5 and –2.0 in association at least 1 clinical risk factor* for osteoporosis • When T-score (vertebral/femural) is between –2.0 and –2.5 also in absence of clinical risk factors for osteoporosis	**Preventive therapy ("high risk osteopenia"):** • When T-score (vertebral/femural) is between –2.0 and –2.5 in association with at least 1 clinical risk factor* for osteoporosis
Therapy of osteoporosis: • In all women with T-score £ -2.5 measured at central skeletal sites (vertebral/femural)	**Therapy of osteoporosis:** • In all women with T-score £ -2.5 measured at central skeletal sites (vertebral/femural)
J.A. Kanis, 1996	
Osteoprotective therapy: When Z-score value is equal or less than a – 1.0**	
* main clinical factors to develop osteoporosis: advanced age (great risk for fracture), fast bone losers (diagnosed by repeated bone densitometry or bone resorption markers), risk factors for bone loss (e.g. hyperparathyroidism, corticosteroid therapy, immobilization, chronic illness), low BMI, prior fracture, family history of "fractured osteoporosis" ** low bone density for the matched age (great life-time risk to develop osteoporosis)	

Study of Osteoporotic Fractures (SOF), Canadian Multicenter Osteoporosis Study (CAMOS), the EPIDOS study, the Rotterdam data, the Dubbo Osteoporosis Epidemiology Study, and other population studies. Other relevant fracture risk factors (which are not completely validated or investigated) are documented (Table IV).

Table III. Risk factors for fractures validated in 8 International Cohorts (60.000 women over 10 years) (WHO Scientific Group Meeting on Fracture Risk Reporting, Brussels, Belgium, May 5-7, 2004) (12

- Femoral neck T-score (bone density)
- Age
- Previous low trauma fracture
- Low BMI
- Current cigarette smoking
- Steroid exposure at any time
- Rheumatoid arthritis
- High alcohol intake (> 2 units/day)*
- Family history of hip fracture

** 1 Unit = 8 gm alcohol = pt beer = glass wine*

Table IV. Other risk factors for fractures

Factors correlated to bone strength:

- Bone geometry
- Microarchitectural
- Proportion of cortical to cancellous bone
- Stress risers
- Efficiency of bone cells
- Level of bone turnover

Factors of propensity to fall:

- Muscle weakness
- Gait deficit
- Balance deficit
- Visual/sensorial deficit
- Chronic disease impairing mental or physical
- Certain medications (sedatives, antidepressants)

The presence of significant fracture risk detected on the basis of the anamnestic or ultrasound data doesn't authorize the prescription of osteoprotective therapy, but only the activation of preventive comportamental measures to change the probability to undergo fractures and to proceed to bone density analysis in skeletal sites specific for bone fragility in woman (vertebrae, hip) to confirm postmenopausal osteoporosis.

Diagnosis of postmenopausal osteoporosis

Diagnosis of osteoporosis is that of a skeletal disease (13). Before introduction of bone DEXA technology and of WHO densitometric criteria, diagnosis of osteoporosis rested onto radiological identification of minimal trauma fractures at skeletal sites of prevalent trabecular (postmenopausal osteoporosis) or cortical bone composition (senile osteoporosis). Radiological imaging allows identification of osteopenia thanks to transparency, but only when more than 30% of bone mass is lost. Introduction of DEXA (Double Energy X-rays Absorptiometry) technology has modified the overall diagnostic approach, demonstrating that bone density is a key skeletal factor for fracture risk and allowing skeletal site-specific diagnosis of postmenopausal osteoporosis at vertebrae and femural neck, according to WHO diagnostic criteria. These advances disclosed the new era of "preventive diagnosis" of postmenopausal osteoporosis leading to precocious diagnosis and timely start of osteoprotective medical interventions ("active prevention"), before the onset of overt clinical osteoporosis.

Bone densitometry DEXA

DEXA is the reference method to diagnose postmenopausal osteoporosis. It employs x-rays generated by a catodic tube, so it is not governed by the rules and regulations associated with radioactive isotopes as in the previous DPA (Double Photon Absorptiometry) technology. It is extremely fast, cause no pain or discomfort, and its radiation exposure is not clinically significant. DEXA measures bone density with extreme accuracy in terms of precision and reproducibility. In clinical practice bone density is expressed per surface unit (g/cm2). In 1994 the World Health Organization (WHO) established DEXA diagnostic criteria for osteoporosis (6) (Table V), widely applied regardless of the skeletal site or of the DEXA machine used to make the measurements, although this is incorrect. WHO criteria classify individuals as normal, osteopenic and osteoporotic on the basis of T-score value, which is based on a comparison of value of bone mineral density (BMD) measurement in any individual patient with the mean BMD obtained in a population of young male or female people. In detail, the T-score is calculated as the difference between the patient's bone density and the mean bone density for the reference young population and is expressed as units of standard deviation of the young population:

$$\text{T-score} = \frac{\text{value of patient BMD - value of mean BMD of young population}}{\text{SD of mean BMD of young population}}$$

Table V. WORLD HEALTH ORGANIZATION

CLASSIFICATION OF BONE DENSITY		
Classification	**T-score**	**Fracture status**
Normal	Greater than –1	Unspecified
Low bone density	Between –1 and –2.5	Unspecified
Osteoporosis	Less than or equal to –2.5	Unspecified
Severe osteoporosis	Less than or equal to –2.5	One or more

Another interesting bone density indicator is Z-score, which is less used in clinical practice but is very useful in the evaluation of the severity of the osteopenia in relation to individual age. The Z-score is the number of standard deviations of BMD of the individual below the age-matched BMD mean.

$$\text{Z-score} = \frac{\text{value of patient BMD} - \text{value of mean BMD of age-matched population}}{\text{SD of mean BMD of age-matched population}}$$

Although Z-score does not allow diagnosis of osteoporosis according to WHO guidelines which quote T scores, it does give some idea of a patient's risk in relation to other patients of the same age. A negative value of Z-score always indicates that the bone density is lower than it should be for the patient's age and sex. A young osteopenic woman with a Z-score below –1.0 will not have a high risk of fractures in the short term, but she will have a high risk in the long-term.
The Z-score is also used to give clinical information on the type of osteoporosis. A Z-score below –1.5 suggests primary osteoporosis, which is age related. A Z-core of –1.5 or lower indicates association between primary factors (aging and/or menopause) and secondary factors (they are detailed in Table I). The relative risk of a fracture changes from 1.5 to 2.5 for each standard deviation below the age-matched mean (i.e. one Z-score unit).
In summary, the established clinical applications of bone density DEXA measurement are:

- Diagnosis of osteoporosis in women without fractures
- Diagnostic confirmation of osteoporosis when fracture has occurred
- Evaluation of osteoporosis and of fracture risk
- Calculation of rate of bone loss to identify fast-losers
- Monitoring of efficacy of osteoprotective therapy

In addition, the bone density DEXA measurements, using WHO diagnostic criteria, permit epidemiological preventive population studies on the incidence of osteoporosis. Using bone vertebral density the prevalence of osteoporosis among an italian sample of climacteric population has been estimated to be about 30% (14).

Quantitative Computed Tomography (QCT)

Before the advent of DEXA, bone density measurements were obtained using computed tomography (CT) scanners in the so called quantitative CT (QCT) to differentiate it from imaging CT (1). QCT reports a volumetric density (in mg/cm3) as opposed to the area density (in g/cm2) of DEXA. Although this should make QCT a potentially useful methodology in the specific diagnosis of trabecular bone osteoporosis, its relatively high cost and the high radiation exposure limits the current clinical use which is reserved to the experimental clinical research protocols, in particular in investigating the central bone region of the vertebral body and femur, i.e. cancellous bone, which is a more sensitive site for detecting bone mineral changes in postmenopause than most other skeletal sites. WHO diagnostic criteria developed for DEXA cannot be applied for QCT.

Quantitative Ultrasound (QUS) technology

Bone quantitative ultrasound (QUS), introduced in the recent years as an investigative tool for osteoporosis, investigates the way that bone attenuates sound waves and/or the speed with which sound travels through the bone. The attenuation of ultrasound results from scattering and absorption of the ultrasound wave. Bone, particularly cancellous bone, is a non homogeneous material and leads to complex scattering of ultrasound waves. Absorption refers to the transfer of energy from sound waves into heat. Ultrasound attenuation in bone can be measured by calculating the linear relationship between amplitude loss of the sound wave with varying sound wave frequencies. The slope of this line is referred to as BUA ("Broadband Ultrasonic Attenuation" expressed as decibels/megahertz [dB/MHz]). The attenuation has been claimed to correlate with histomorphometric parameters of trabecular structure. An additional parameter reported by QUS is the SOS ("Speed of Sound", expressed as m/s). SOS is directly related to the elasticity and thereby provides unspecific information on density of the bone, through the derived ultrasound parameters "stiffness index" or "BMD equivalent" which combine BUA and SOS to incorporate both ultrasound parameters. QUS does not measure bone mineral content and should be categorized separately from the other densitometric technologies. Even if QUS measures are not highly correlated with measures of bone density made by DEXA, some *in vitro* studies, but not all, suggest that QUS might reflect other aspects of bone structure that could be associated with bone fragility. QUS devices are presently not capable to measure skeletal sites specifically involved in the postmenopausal osteoporosis (i.e. vertebral or distal femur), and even if osteoporosis is referred as diffuse skeletal pathology, site-specific measurements (i.e. neck femur BMD for neck femur osteoporosis) are essential to diagnose the postmenopausal osteoporosis syndrome. Recent personal data confirm the poor accuracy of the peripheral ultrasound to select women diagnosed osteoporotic by DEXA at vertebral or hip (15). The full potential of this technology cannot be realized without additional studies on the precision, accuracy, reproducibility, and appropriateness of ultrasound densitometry in the clinical setting. The actual clinical application of QUS methodology is in the evalutation of the fracture risk, when combined with anamnestic risk factors to capture "high risk" women candidate to DEXA analysis for confirmation of postmenopausal osteoporosis in *"selective screening programs"* (16). WHO diagnostic criteria are not valid for the new quantitative ultrasound methodologies.

Bone metabolic markers in postmenopausal osteoporosis

Both formation and resorption markers are of value in estimating bone turnover rates. Postmenopausal osteoporosis is due to an increase of the osteoclast activity that is linked with an increase of bone formation not compensating the increased resorption activity. As consequence, bone turnover rate increases in postmenopause and correlates negatively with bone density that decreases. However, correlation of biochemical markers with bone density is very poor, because of high day-to-day variations so that they are not useful in diagnosing osteoporosis, but may be used to identify fast bone losers at high risk for osteoporosis (17). From population studies, it appears also that markers of bone resorption (as collagen type I cross-linked N telopeptide – NTx) may be useful predictors for fracture risk and bone loss. Elevation in bone resorption markers may be associated with an increased fracture risk in elderly women. However, the predictive value of biomarkers in assessing the individual women has not yet been confirmed. Biomarkers measurements are also currently limited in diagnostic use by their high variability (± 30%) within individuals. In conclusion, bone turnover markers should not be used in diagnosis of postmenopausal osteoporosis. Their diagnostic potentiality should be limited to assessment of fracture risk in a wider diagnostic panel and additional studies are still necessary to confirm their possible use in individual patients to select fast losers at high risk for osteoporosis.

A practical approach for diagnosis

Gynecologyst have a golden opportunity for prevention of postmenopausal osteoporosis because they care women at the perimenopausal

transition, the ideal period of life to assess bone status to avoid late clinical skeletal involvement. In this perspective physicians should proceed through assessment of risk factors (both for osteoporosis and fracture) and eventually densitometric diagnosis in women at "high risk". A practical query: when to prescribe bone density examination ? when to repeat it ?

When to prescribe bone density examination

All women undergo postmenopausal estrogenic deprivation. This represents the main osteoporosis risk factor for the female population. Therefore, theoretically, all women should be informed about the bone status by DEXA analysis before rapid perimenopausal bone loss takes place in order to start timely a preventive treatment. The right time for the first densitometric assessment at spine (the more sensitive skeletal site to estrogen deprivation) should be at the perimenopausal transition at which signs of endocrine ovarian instability appear and concomitantly rate of bone loss accelerates. This allows (i) to scrutiny bone mineral content before postmenopausal loss (remember that up to 30% of premenopausal bone mass can be lost during the first 4-5 yrs after menopause); (ii) to identify timely severely osteopenic (not yet osteoporotic) women at "high risk" for bone fragility who should be administered bone protective therapy.

This ideal protocol would imply to submit all women at perimenopausal transition to bone densitometric evaluation by DEXA, but this approach is not feasible at the population level because of the unfavorable high cost/benefit ratio (although this choice can be adopted at individual level by physician). In this optics scientific societies and health authorities state guidelines providing useful clinical-anamnestic parameters within "screening programs" to select for DEXA women at high risk. This issue is particularly relevant after the publication of the WHI study (18) and the consequent decline in the number of postmenopausal women using HRT which protects against osteoporosis.

When to repeat bone density examination

We should distinguish two different conditions depending on whether women are submitted or not to osteoprotective therapy.

Women not undergoing osteoprotective therapy should be re-assessed (i) after 3-5 years if they are not osteopenic or are not at "high risk" for osteoporosis; (ii) after 2 years if they have significant osteopenia or high risk factor for accelerated bone loss (e.g. during the earlier years after menopause especially in the case of bilateral ovariectomy (3); (iii) after even longer time in patients who have an initial BMD measurement well above the minimal desirable level.

In the case of women on osteoprotective therapy, measurement of bone density should be repeated at least once to monitor the response to therapy for bone loss 1-2 years or longer after starting the therapy. Monitoring therapy response at intervals of less than 1-2 years is considered methodologically not correct. This is a consequence of the expected slow changes in bone mineral density (-1.5% yearly) and of the precision error of bone measuring technologies which overlap each other.

THERAPEUTIC MANAGEMENT

The approach to the prevention and treatment of osteoporosis has changed significantly in the recent years. Medical prevention and treatment of postmenopausal osteoporosis started in the late '80s at the time when clinical notion of osteoporosis changed from a clinical "fractured syndrome" to "densitometric syndrome" with the definition of bone fragility based on the WHO diagnostic densitometric criteria of bone vertebral/femural by DEXA (Table V) (6). As physicians realized that this condition is largely dependent on estrogenic deficiency, HRT emerged as ideal protective therapy. This orientation was challenged as consequence of recent large population trials (Women Health Initiative and Million Women Study) (18, 19) directed to investigate benefits and risks of HRT. These investigations evidenced risks of this long term therapy to increase occurrence of breast cancer and cardiovascular disease and brought about a discontinuation in the use of HRT as long-term osteoprotective treatment, at least in the absence of severe subjective symptoms of estrogenic deprivation.

However, now we have two main alternatives for medical management of osteoporosis, either a hormonal estrogen treatment or the administration of specific osteoprotective drugs as bisphosphonates and SERMs. The choice between these alternatives is certainly a time-consuming one requiring by the gynecologist a dedicated clinical assessment of the patient in the perspective of therapy/prevention or in the treatment of osteoporosis as a facet of the more complex "menopausal syndrome". This concept can be marked as therapy of the pathology (i.e. osteoporosis) versus therapy of the patient (i.e. "osteoporotic menopausal women"), projected into the whole health needs of the climacteric woman. This comprehensive approach translates the concept of "personalized approach" to the global menopausal syndrome to avoid also diagnostic and therapeutical over- and mis-prescriptions for the several hormonal problems that can affect climacteric women, to increase compliance and adherence to the treatments and to reach the final target of the woman health care.

Who should be treated and when: prevention and therapy

If drugs and hormones were 100% efficacious, 100% safe and cost-free, and the women were 100% compliant, the answer would be to treat everyone and early. As this is not the case, the most important factors determining whom and when to treat are (i) the diagnosis of osteoporosis in absence of fracture ("densitometric osteoporosis") or in presence of an osteoporotic fracture(s) ("severe osteoporosis") and (ii) the selection of women at "high risk" for osteoporosis on the basis both of clinical factors and of bone densitometric measurement (some criteria to identify these "high risk" women are reported in Table II). Only women in these two groups should be treated with drugs or hormones (20-22).

Historicals of the osteoprotective validated therapies for postmenopausal osteoporosis

Between 1984 and 1995, estrogen (Hormonal Replacement Therapy) and injectable synthetic salmon calcitonin were the only agents approved in the USA for prevention and treatment of postmenopausal osteoporosis. Within the past several years, however, the number of the management options has expanded significantly. In late 1995, the FDA in USA approved the use of oral alendronate (10 mg daily), the first bisphosphonate recognized as effective for the treatment of postmenopausal osteoporosis. The FDA also approved a lower dose of alendronate (5 mg daily) for the prevention of osteoporosis in the "high risk" osteopenic women. Early in 1997, raloxifene became the first selective estrogen receptor modulator (SERM) approved for the prevention of postmenopausal osteoporosis, with subsequent approval for the treatment of osteoporosis in late 1999. In early 2000, risedronate (5 mg daily) became the second bisphosphonate approved for the prevention and treatment of osteoporosis. In late 2000, the weekly administration of alendronate (70 mg for therapy of osteoporosis and 35 mg for prevention) was also approved with the subsequent approval by FDA of weekly risedronate (35 mg) in May 2002. All above cited agents are essentially antiresorptive drugs. Latest news came in November 2002, with the approval by

FDA of the first anabolic osteoformative agent, a truncated form of parathyroid hormone (PTH), called teriparatide (rPTH (1-34), 20 mcg administered subcutaneously each day) and in June 2004 with the approval by European Medicines Evaluation Agency (EMEA) of the strontium ranelate a new treatment for postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. Strontium ranelate is reported both to reduce bone resorption and to stimulate bone formation. Finally, recent evidences seem to indicate that oral clodronate at high dosage (800 mg/day) is capable to reduce risk fracture in women affected by vertebral osteoporosis. All the osteoprotective therapies for postmenopausal osteoporosis, with the exception of the recently approved teriparatide and strontium ranelate, act primarily by inhibiting bone resorption.

Selection of drugs for active prevention and therapy of postmenopausal osteoporosis

We must take into account several criteria (Table VI) when seeking the appropriate medical management in the perspective of prevention or therapy of osteoporosis in climacteric woman:

(i) *the entire clinical picture of the menopausal syndrome*: in presence of severe symptom(s) or problem(s) (vasomotor, urogenital) related to estrogen-deficiency status, Hormonal Replacement Therapy (HRT) is the appropriate osteoprotective choice.

(ii) *the specific skeletal indication for therapy*: while all osteoprotective therapies are demonstrated to be efficient in reducing the osteoporotic risk (maintaining/increasing bone density), not all therapies are clinically validated for the treatment of osteoporosis to reduce fracture risk. In addition, not all therapies are capable to reduce fracture risk at all skeletal sites involved in postmenopausal osteoporosis

(iii) *the individual therapeutic risk*: every approved osteoprotective therapy for postmenopausal osteoporosis is charged with a therapeutic risk documented by epidemiological population studies. The decision to prescribe a specific therapy must consider the epidemiological therapeutic risk information projected into the therapeutic risk profile of the individual patient.

(iv) *the additional benefits* of the osteoprotective therapy in relation to the individual clinical picture

(v) *dosage*: it should be the minimal dose effective for the therapeutic target

Duration of osteoprotective therapy for postmenopausal osteoporosis

Osteoprotective therapy for osteoporosis is *per se* a "long-term therapy". In case of HRT, duration of therapy will be linked to the persistence of the estrogen deficiency symptoms verified during a HRT suspension period. If the HRT is suspended definitively and the osteoporotic risk is still present, it will be necessary to continue with an alternative osteoprotective therapy.

Table VI. FDA approved hormones/drugs for postmenopausal osteoporosis

"Active prevention" (in women diagnosed osteopenic at "high risk" to reduce osteoporosis risk)	**Therapy** (in women diagnosed osteoporotic to reduce fracture risk)	**Additional benefit**
- HRT		Relief of vasomotor and urogenital disturbances
- Raloxifene	- Raloxifene *(only for vertebral osteoporosis)*	Decrease in cholesterol level and breast cancer risk
- Alendronate 35 weekly * *(or alendronate 70 every 15 days)*	- Alendronate 70 weekly	None
- Risedronate 35 weekly	- Risedronate 35 weekly	None
	- PTH	None
* available in USA		

Detection of therapeutic efficacy

During the use of osteoprotective therapy in osteopenic "high risk" women as "active prevention" for postmenopausal osteoporosis, measurement of bone density by DEXA is probably an adequate tool to check therapeutic efficacy. However, bone density analysis has limitation due to requirement of long time intervals (1-2 yrs) to obtain reliable response on the efficacy of therapy. This time lag is dependent on the entity of method reproducibility error and on expected change of bone density during time. An additional approach is represented by determination of bone metabolic markers which (i) correlate significantly to bone loss, (ii) seem to identify more responders to therapy than bone density and (iii) respond earlier to therapy than bone density. For these reasons bone markers has been proposed to verify osteoprotective efficacy (23). In particular, bone resorption markers is recommendable in predicting and monitoring response to antiresorptive therapy in study group clinical trials. Some authors think that these markers should be measured in individual women before and after starting therapy to identify non-responders or non-compliant patients. Data from group studies consistently show a decrease of either NTx or CTx resorption markers by about 20% with estrogen therapy and by 40-60% with alendronate after 3-6 months of therapy. Because of the high variability of these biomarkers only the individual response to alendronate therapy can be monitored with accuracy. Reduced levels of these markers appears to correlate with a low incidence of vertebral fractures in observational studies. In relation to variation of markers during therapy we must underline that they are not always predictive of responsiveness, even if recent data confirm that changes at 6 months predict improvement in bone density at spine and hip at 3 years in elderly women on alendronate, HRT or combination therapy (23).

During administration of drugs/hormones in diagnosed osteoporotic women to reduce fracture risk we can't measure the change in this risk, and we usually use again bone density as skeletal surrogate endpoint of fracture risk. At this purpose, we should remind that density is not the only parameter to explain efficacy of osteoprotective therapies in reducing fracture risk. In fact, currently validated therapies for osteoporosis provide fracture protection that is larger than that predicted from the rather modest increase in bone density. Relevant changes in bone quality probably should be invoked to explain completely the reduction in incidence of fractures. The exact microarchitectural basis for this quality improvement remains unclear, since there is no diagnostic validated test to assess this skeletal parameter. Bone metabolic assessment and ultrasound analysis could give additional information on this structural effect. In particular, evidences indicate that changes in bone turnover are related to reduction in vertebral fracture incidence (24).

CONCLUSION

Postmenopausal osteoporosis represents only one piece of the more complex "menopausal syndrome". The postmenopausal estrogenic deficiency plays a key role in the pathogenesis of this devasting disease. The main diagnostic and therapeutic target for the physician is the prevention, by selecting osteopenic women diagnosed at "high risk", but not yet osteoporotic, on the basis of anamnestic and densitometric parameters already during the peri-menopausal years to start preventive therapy. The diagnostic intervention should include combined clinical, instrumental and laboratory data. The therapeutic choice should also take into account the contemporaneous presence of other symptoms of estrogenic deficiency. HRT represents the first-line therapy for prevention of osteoporosis in the presence of other estrogen deficiency symptoms. In their absence, specific alternative osteoprotective therapies should be considered, as bisphosphonates (alendronate, risedronate) and SERMs (raloxifene). Because a long-term therapy is required to achieve therapeutic efficacy in postmenopausal osteoporosis, it is mandatory to assure high compliance and adherence for any type of medical treatment. Any pharmacological intervention has inherent therapeutic risk, which can be minimized referring to both the documented toxicity of the drug and the individual clinical presentation of the patient. Only a correct diagnostic and therapeutic approach might represent the right guideline to achieve the preventive goals (reduction of osteoporosis and of fracture risk) to improve the women quality of life and to reduce the high individual and social costs of this pathology.

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